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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
FOSTER, CHRISTINE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,298	BERGMANN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008 and 30 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *12-14,17,18 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15,16,19-29,31 and 32* is/are rejected.

7)☒ Claim(s) *1-7, 10, 19, 21-23, 25-27, and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/23/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendments, filed on 9/29/2008 and in the corrected Reply of 12/30/2008, are acknowledged and have been entered. Claims 1-18 were amended. New claims 19-32 have been added.

Election/Restrictions

2. Newly submitted claim 30 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The newly presented claim is directed to a product, namely an isolated peptide consisting of the amino acid sequence of SEQ ID NO:3. The originally presented claims recited methods for determination of adrenomedullin. Although the claims are related to the product claims in that the product may be used in the detection methods, they are nonetheless patentably distinct because the product may be used in distinct methods, such as an immunogen in a method for producing antibodies against mid-pro AM.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 30 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Accordingly, claims 1-32 are pending in the application, with claims 12-14, 17-18, and 30 currently withdrawn. Claims 1-11, 15-16, 19-29, and 31-32 are subject to examination below in light of the elected species of **cardiac disease**.

Priority

4. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP04/00806, filed 1/29/2004, which claims priority under 35 U.S.C. 119(a)-(d) to Application No. 103 16 583.5, filed on 4/10/2003 in Germany.

Objections/ Rejections Withdrawn

5. The objections to the specification not reiterated below have been withdrawn in response to Applicant's amendments.

6. The objections to claims 2-11 and 15-16 as set forth in the previous Office action have been obviated by Applicant's amendments thereto.

7. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn in response to Applicant's amendments.

8. The rejections of claims 1 and 15-16 under § 102(b) as being anticipated by Bergmann et al., and of claims 2-11 under § 103 as being unpatentable over Bergmann et al. have been withdrawn in response to Applicant's persuasive arguments (see Reply, especially at page 14, second paragraph to page 15).

Specification

9. The disclosure is objected to because of the following informalities:

10. The word "chemiluminescent" is misspelled on page 17, line 1.

11. The heading "The Brief Description of the Drawings" is not present in the specification. A reference to and brief description of the drawing(s) is required as set forth in 37 CFR 1.74. See MPEP § 608.01(f).

12. On page 9, lines 1-2 refer to 'amino acids 45-**95** of pre-proAM (SEQ ID NO:3)", which appears to be a typographical error or 45-**92**.

Incorporation by Reference

13. In the instant Reply, Applicant points to U.S. 2004/0180396 and WO 00/22439 as providing support for new claims 20-21 and 31 (Reply, page 11).

14. The attempt to incorporate subject matter into this application by reference to U.S. 2004/0180396 is ineffective because the specification does not:

(1) Express a clear intent to incorporate by reference by using the root words "incorporat(e) " and "reference " (e.g., "incorporate by reference "); or

(2) Clearly identify the referenced patent, application, or publication.

See MPEP 608.01(p). In the instant case, U.S. 2004/0180396 is not mentioned at all in the present application.

15. The attempt to incorporate subject matter into this application by reference to WO 00/22439 is ineffective because:

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office.

The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

In addition, the specification does not express a clear intent to incorporate by reference by using the root words "incorporat(e) " and "reference " (e.g., "incorporate by reference ").

16. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Claim Objections

17. Claims 1-7, 10, 19, 21-23, 25-27, and 32 are objected to because of the following informalities:

18. Applicant is requested to employ consistent spelling of the term mid-pro AM in claims 1-4, 10, 19, 21-23, 25-27, and 32 (i.e., either mid-pro AM, mid-pro-AM, or mid-proAM).

19. Claim 2 recites that mid-proAM is measured in an immunoassay which operates with "at least one labeled antibody which specifically recognizes a sequence of mid-proAM". This antibody appears to refer back to the same antibody which is earlier recited in claim 1 ("a monoclonal or polyclonal antibody which in each case is specific only to said partial peptide"), but this is not made explicit. The claim is confusing because the relationship of the antibody of claim 2 to that previously recited in claim 1 is not made clear.

20. Similarly, in claim 3 it would seem that the "labeled antibody" and the "at least two antibodies" are intended to further limit the antibodies earlier recited in claims 1-2, but this is not clear.

21. Similarly, claims 6 and 7 recite that "all antibodies" are monoclonal and/or polyclonal or are affinity-purified polyclonal antibodies, respectively. It appears that Applicant intends that "all antibodies" refers to the "labeled antibody" and to the "at least two antibodies" which are mentioned in claim 3, but this is not made clear. Applicant is requested to amend the claim(s) for clarification.

22. Regarding the abbreviation "pre-proAM" in claim 5, it is suggested that in the first instance of an abbreviation in the claims that the abbreviation be accompanied by the full term.

23. In claims 19, 21-22, 25-27, and 32, "SEQ ID NO 3" should read "SEQ ID NO:3" for consistency.

24. The term "pro-adrenomedullin" in the last line of claim 19 should apparently read --proadrenomedullin-- in accordance with line 3 of the claim.

25. Claim 23 recites "**A** method of claim 22". The language --**The** method of claim 22-- is suggested in order to avoid ambiguity.

26. Claim 27 has a typographical error of "mid-regional" in the second-to-last line of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

27. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claims 1-11, 15-16, 19-29, and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

29. Claim 1 now recites that the measuring "uses a monoclonal or polyclonal antibody which in each case is specific only to said partial peptide". Applicant's Reply states that no new matter has been added and indicates that support may be found for the claim amendments on page 6, line 7 to page 7, line 5; at the paragraph bridging pages 8-9; and at page 14, lines 10-15 (Reply of 9/29/2008 at page 11). The Examiner was unable to find support where indicated.

Although the specification discloses the use of an antibody that specifically recognizes a sequence of mid-proAM (see, e.g., original claim 2), support could not be found for the limitation that the antibody is specific only to this partial peptide.

In the instant case, because the amino acid sequence defined by mid-proAM is entirely contained within the larger precursor molecules pro-adrenomedullin and prepro-adrenomedullin, this means that all of the amino acids in mid-proAM are also shared by pro-adrenomedullin and prepro-adrenomedullin. Consequently, it is to be expected based on the disclosure that antibodies that bind to the mid-proAM would also bind to pro-adrenomedullin and prepro-adrenomedullin. Therefore, no implicit support is apparent for the limitation that the antibodies are specific *only* to mid-proAM.

In addition, it was well known in the art at the time of the invention that antibodies do not contact the entire surface of their target antigen but rather bind relatively small regions or "epitopes" within said antigen. See Wolfe (Wolfe, S.L., Molecular and Cellular Biology, 1993, pages 790-793), which discloses that the size of an epitope bound by an antibody is between 3 to 16 amino acids in length (see particularly the bottom of the left column of page 791).

A well-known immunological phenomenon known as **cross-reactivity** arises due to this nature of antigen-antibody binding. As evidenced by Kuby (Immunology, W.H. Freeman and Company (1992), page 125):

> "Although the antigen-antibody reaction is highly specific, in some cases antibody elicited by one antigen can cross-react with an unrelated antigen. Such cross-reactions occur if two different antigens share an identical epitope or if antibodies specific for one epitope also bind to an unrelated epitope possessing similar chemical properties."
>
> See the left column of page 125.

As a consequence, antibodies can be specific and yet still cross-react with antigens other than those used to generate the antibodies. For example, Bendayan (J. Histochem. Cytochem. 1995; 43:881-886) teaches that the specific reactivity of a monoclonal antibody can be highly

specific yet cross-react with antigens from different species or even distinct proteins not related to the original antigen (see page 886, last paragraph). Similarly, Bost et al. (Immunol. Invest. 1988; 17:577-586) teach antibodies which "cross-react" with both IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (e.g., "Results, page 579).

In the instant case, the specification states only that the antibodies are specific for mid-proAM but does not disclose that the antibodies would not be specific for any other molecule. In view of the nature of antigen-antibody binding and in particular in view of the well-documented phenomenon of cross-reactivity, one skill in the art would not envisage that the antibodies specific for mid-proAM would bind only to this peptide and not to any other molecule. Rather, it would be expected that such antibodies would bind to other species that also share identical or related epitopes with mid-proAM.

For these reasons, neither explicit nor implicit support is apparent for the limitation that the antibody is "specific only to said partial peptide" as now claimed.

30. New claim 19 recites that the measuring "uses a monoclonal or polyclonal antibody which in each case is specific to an epitope in said partial peptide sequence and not to any other epitope of pro-adrenomedullin". Applicant's Reply states that no new matter has been added and indicates that support may be found for the claim amendments on page 6, line 7 to page 7, line 5;

at the paragraph bridging pages 8-9; and at page 14, lines 10-15 (Reply of 9/29/2008 at page 11). The Examiner was unable to find support where indicated.

The specification does not provide explicit support for the noted limitation. Although it can be assumed that the disclosed antibodies which are specific for mid-proAM (SEQ ID NO:3) bind to epitopes therein, there is insufficient evidence to conclude that such antibodies would inherently not also bind to any other epitope of pro-adrenomedullin.

As taught by Wolfe (discussed above), antibody epitopes may be as short as 3 amino acids in length. In view of the well-documented phenomenon of antibody cross-reactivity discussed above, antibodies that are specific to epitopes in mid-proAM could also bind to epitopes of pro-adrenomedullin. The mid-proAM peptide includes the 3-amino acid sequence AGP (residues 61-63 of SEQ ID NO:1), which is also present in amino acids 156-159 of pro-adrenomedullin (SEQ ID NO:1). Because mid-proAM shares sequences in common with other regions of the pro-adrenomedullin molecule of length on the order of typical antibody epitopes, it cannot be concluded that antibodies that bind to mid-proAM would necessarily and always not also bind to other epitopes within the pro-adrenomedullin molecule as now claimed.

In addition, claim 19 encompasses a polyclonal antibody which is specific to "an epitope in said partial peptide sequence and not to any other epitope of pro-adrenomedullin". This implies that the antibody is specific to a single epitope in mid-proAM.

However, polyclonal antiserum was well known in the art to comprise a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen. See the Academic Press Dictionary of Science and Technology, which defines a polyclonal antibody as a population of heterogeneous antibodies derived from multiple clones,

each of which is specific for one of a number of determinants found on an (definition for the term "polyclonal"; Oxford: Elsevier Science & Technology (1996); retrieved October 22, 2008, from http://www.credoreference.com/entry/3144515/). See also Janeway et al. (Immunobiology: the Immune System in Health and Disease (1999), Elsevier Science Ltd/Garland Publishing, New York, NY, Fourth Edition, pages 34-35), which provides evidence that antibodies in serum (i.e., antisera) are polyclonal in nature, containing many different antibody molecules that bind to an antigen in many different ways (see p. 34-35, especially at p. 35, the second full paragraph, and Figure 2.1).

In view of such facts, one skilled in the art would not envisage possession of a polyclonal antibody that is specific to "an" epitope of mid-proAM, as polyclonal antibodies comprise a heterogeneous population which recognizes a number of different epitopes on antigens.

For all of these reasons, neither explicit nor implicit support is apparent for the limitation that the antibody is "specific only to said partial peptide" as now claimed.

31. Claim 9 now recites that one of the antibodies is "**not bindable to a solid phase**". Applicant's Reply does not specifically indicate where support for the noted limitation may be found, and the Examiner was unable to find support in the specification or claims as originally filed. MPEP 2173.05(i) states:

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187,196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112,

first paragraph, as failing to comply with the written description requirement.

In the instant case, the limitation that the antibody is not "bindable" is not disclosed in the application as filed (this term does not appear in the specification). Original claim 9 recites that the antibody "is bound to a solid phase". Thus, support may be found for an exclusionary proviso wherein the antibody "is not bound to a solid phase".

However, the claim recites that the antibody is not "bindable" to a solid phase. This terminology would also encompass not only antibodies which are not currently bound to a solid phase, but those which are incapable of becoming bound by any means. This conveys a different scope than antibodies which are simply not bound to a solid phase. For example, this claim language would encompass antibodies that are incapable of binding to a solid phase even by adsorption. Support for such antibodies that would be incapable of being bound to a solid phase could not be found in the specification.

Although claim 9 as originally filed also recited that the antibody "can be bound to a solid phase", the scope and meaning of this language was not clear as it is not a positive recitation (see rejection under § 112, 2nd paragraph below). Consequently, this statement is not considered to be a positive recitation of antibodies that are "bindable" to a solid phase; it could also be read as meaning as above that the antibodies are bound to the solid phase.

32. New claim 23 recites that the "measured level of said partial peptide…has an order of magnitude which is greater than the order of magnitude of 2X times said level in a healthy person". Applicant indicates support for the noted limitation at page 6, line 7 to page 7, line 5.

The noted passage discusses the observed increase in sepsis patients as compared to healthy subjects when measurements were conducted with a commercially available radioimmunoassay. This prior art radioimmunoassay gave a measured increase "only of the order of magnitude of about twice the normal value".

Using the disclosed methods, Applicant observed for some patients increases in mid-proADM levels which were greater than 2X those of some healthy subjects (Figure 1). However, these observed increases represent *precise data points* for each individual studied. By contrast, the limitation that the measured levels are "greater than the order of magnitude of 2X" invokes a *range*; and in particular a range that has *no upper limit*. This causes the claim to read on embodiments in which the measured values are, e.g., 5000 times higher than those in healthy subjects. The amendments therefore represent new matter because they change the scope of the original disclosure. MPEP 2163.05 (III) and also In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

33. New claim 24 recites that the human from whom the biological fluid sample is taken is "not suspected of suffering from sepsis". Applicant's Reply states that support for the new claim may be found at page 14, lines 16-25 (Reply, page 11), which discloses:

> The measurement of sera of patients by means of an assay which specifically measures this mid-proAM gives measured results which not only permit a clear distinction between sepsis patients and normal persons but--in combination with clinical findings--also enable the detection of other diseases which are associated with increased formation of AM, in particular cardiac and cancer diseases.

This passage mentions "sepsis patients" but does not disclose patients "suspected of suffering from sepsis". No support could be found for the limitation that the method is performed

on subjects "suspected of suffering from" or alternatively "not suspected of suffering from" sepsis.

34. New claim 26 recites a method for determination of adrenomedullin release in a human "suspected of having a disease, other than sepsis, associated with an increased level of adrenomedullin release". Similarly, new claim 27 recites a method for the diagnosis of a disease "other than sepsis which is associated with an increased level of adrenomedullin release". Applicant's Reply states that support for the new claim may be found at page 6, line 7 to page 7, line 5. In the noted passage, the specification discloses that increased levels of adrenomedullin were observed in sera of sepsis patients using a prior art assay.

However, the genus of "a disease, other than sepsis, associated with an increased level of adrenomedullin release" is not disclosed. Although the specification does positively recite sepsis patients, this does not correspond with the subject matter now excluded by the negative proviso. Rather, the claims encompass performing the assay method on subjects *suspected of having a disease that is associated with an increased level of adrenomedullin release* (and which is not sepsis).

The specification does not disclose the genus of "diseases associated with an increased level of adrenomedullin release". The specification discloses other diseases such as cancer; however, the concept of this genus is not introduced. Consequently, the new claim broadens the scope of the original disclosure as it would encompass not only the other named diseases such as cancer, but any non-disclosed disease that may be subsequently found to be associated with increased level of adrenomedullin. With the exception of those diseases specifically named, one

skilled in the art cannot envisage what other diseases might also be associated with an increased level of adrenomedullin release.

In addition, no support could be found for subjects "suspected of having a disease".

35. Claim 32 recites that the measuring "is not accomplished using a radioimmunoassay requiring an extraction step". Applicant's Reply states that support for the noted subject matter may be found in paragraphs 71 and 73 of U.S. 2004/0180396, which is the U.S. counterpart of WO 00/22439, a document which is in turn referred to in the instant specification (Reply, page 11).

It appears that Applicant acknowledges that support for the noted limitation does not appear in the instant specification. Applicant cannot rely on the disclosures of U.S. 2004/0180396 or WO 00/2243 for support because the essential material therein has not been properly incorporated by reference (see *Incorporation by Reference* above).

36. The claims now refer to a method for the determination of adrenomedullin "release", wherein the level of mid-proAM is indicative of the level of adrenomedullin "release". See claims 1, 15-16, 19, 21-22, 25-27, and 32. As originally filed, the claims recited a method for determination of adrenomedullin "immunoreactivity". The specification does not employ the terminology adrenomedullin "release" in the context of the claimed assay methods, and it is not clear what is meant by adrenomedullin "release" (see rejection under § 112, 2nd paragraph below).

The specification does refer to adrenomedullin being "released into the circulation" in an inactive form (page 3, lines 15-16), but it is unclear whether this is the same context intended by the claims. In addition, the claims are not limited to determination of release into circulation as they are not limited to assay of biological fluid samples which are blood.

The terminology of adrenomedullin "release" introduces new concepts not clearly disclosed in the specification as filed, since it might also imply determination of adrenomedullin release from its larger precursor molecule, secretion from cells, release from a binding partner that is complexed with adrenomedullin, excretion from the body, etc.

37. Claim 22 recites a method of "measuring the level in a biological fluid sample…wherein said measuring is of the circulating level of said partial peptide". As best understood, Applicant intends "the circulating level" to refer to the level in blood. However, the assay does not require that the biological fluid sample be blood. As such, Applicant is now claiming methods in which the blood levels of the partial peptide can be measured through measurement of the partial peptide in other types of biological fluids. No support for such methods could be found in the specification.

One skilled in the art would recognize that not all proteins are expressed in all types of samples; and that even if a protein is expressed in different body fluids, the amounts in each may not correlate. For example, it is also known that the presence of proteins in plasma does not always correlate with their levels in urine, for several reasons. While small solutes such as sodium and urea pass into the urine freely, the kidney generally filters larger molecules including proteins, preventing them from appearing in the urine. This means that proteins that appear in

plasma may not be present in urine; this is particularly true for larger proteins. As one example, Tikhonov et al. (Neph. Dial. Transplant. 12(12):2557-61 (1997)) evaluated levels of IL-8 and defensin in plasma and urine in populations of subjects with pyelonephritis and glomerulonephritis and found that "there was no correlation between urine and plasma levels of IL-8" (see page 2560, left column). Likewise, "[n]o correlation was found between urine and plasma defensin concentrations" (ibid).

For these reasons, one skilled in the art would not envisage possession of methods as now encompassed by the claim in which any body fluid sample is assayed in order to indicate blood levels.

38. Claims 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention relates to an immunoassay method for measuring the level of mid-proAM. The specification discloses that as compared to healthy subjects, measured levels were higher in patients with sepsis, cardiac diseases, and cancer (see Figure 2 and [0075] of the published application).

The claims at issue recite methods for the diagnosis of a disease "other than sepsis", wherein the level of mid-proAM (or a peptide that "has" this sequence) is measured. See claim 27. When the claims are given their broadest reasonable interpretation, they would encompass methods in which diagnosis is made based on the measured levels alone. In addition, the

specification defines "diagnosis" so as to encompass prognosis or monitoring of disease [0002]. As such, Applicant is claiming methods in which the measured levels can be used to diagnose, prognose, or monitor any disease other than sepsis.

The claims further recite that the disease to be diagnosed is "a" cancer or "a" cardiac disease (claims 28-29). This implies that different types of cancer and cardiac disease are encompassed, i.e. that diagnosis of a particular form of cancer or of a particular type of cardiac disease is made.

The data presented in the specification indicate that measurements were higher in patients with sepsis, cardiac diseases, as well as cancer when compared to healthy controls, suggesting that mid-proAM is not specific to any one disease, but rather is elevated in a number of different diseases.

However, there is no guidance with regard to *differential* diagnosis of disease. Rather, all of the examples in the specification relate to subjects whose disease condition was already known, i.e., those subjects who were already diagnosed with the disease. As a result, one skilled in the art would not know, upon observing elevated mid-proAM levels in an unknown subject, whether to diagnose a subject with sepsis, a cardiac disease, a cancer, or some other disease.

A large number of cardiac disorders are known in the art, which may differ substantially in etiology, pathology, and course of disease. See for example Merck Manuals Online Medial Library (section index for "Heart and Blood Vessel Disorders"; Home Edition, retrieved from www.merck.com/mmhe on 3/29/08), which teaches that disorders of the heart include abnormal heart rhythms such as atrial fibrillation; aneurysms; atherosclerosis; cardiomyopathy; pericarditis; and cancerous tumors of the heart.

Although the specification does not provide details regarding the patient population studied, it appears that the patients studied had various types of cardiac diseases (see Figure 2, which refers to "cardiac diseases" in the plural). Since mid-proAM is apparently elevated in multiple types of cardiac disease (in addition to non-cardiac diseases), no basis is seen by which "a" particular cardiac disease could be diagnosed based on mid-proAM levels. Similarly, no basis is apparent by which "a" particular cancer could be diagnosed.

With respect to *prognosis* of disease, there are no working examples in which levels of mid-proAM were correlated with prognosis of any disease. For example, there are no data provide to show that mid-proAM levels differ to a statistically significant degree among subjects who later died of their disease vs. those who survived. The specification fails to provide guidance with regard to how to use mid-proAM levels for prognosis of any disease.

Consequently, further experimentation would be necessary in order to first determine whether mid-proAM measurements could in fact be used for diagnosis or prognosis, i.e. whether levels might be correlated with disease and/or indicative of future morbidity or mortality. This would mean conducting large-scale clinical trials in order to compare the levels in both control and disease patients, and to determine whether statistically significant changes are observed. Since Applicant is broadly claiming diagnosis and prognosis of all diseases (except sepsis), such studies would need to be conducted for each disease.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In the instant case, Applicant has argued that "[i]t was not heretofore known that the mid-regional partial peptide even existed in human blood" (see the instant Reply at page 16, last paragraph). In view of the fact that little was apparently known about the peptide, the limited data presented in the specification do not bear a reasonable correlation to the scope of the claims.

39. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

40. Claims 1-11, 15-16, 19-29, and 31-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

41. Claims 1, 19-23, 25-26, and 32 recite methods in which "the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of (SEQ ID NO:3) and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1)" is measured. This renders the claim indefinite because it employs both open and closed transitional language in describing the peptide that is measured. The claims first recite that the peptide "has" the sequence of SEQ ID NO:3, which is interpreted as meaning that the peptide

must include this sequence but may include additional amino acids on either end. However, the claims also recite that the partial peptide that is measured "consists of" amino acids 45-92, which imply detection only of this 48-amino acid peptide. Accordingly, the metes and bounds of the claims are unclear because it is not clear whether the methods detect SEQ ID NO:3 or alternatively SEQ ID NO:3 and any peptide that comprises SEQ ID NO:3.

42. Claims 1, 15-16, 19, 21-22, 25-27, and 32 refer to a method for the determination of adrenomedullin "release", wherein the level of mid-proAM is indicative of the level of adrenomedullin "release". The specification does not describe determining adrenomedullin "release" and is not clear what is intended by this terminology—release from or into what? This terminology might imply determination of adrenomedullin release from its larger precursor molecule, secretion from cells, release into blood circulation, release from a binding partner that is complexed with adrenomedullin, excretion from the body, etc. Absent a specific or limiting definition of this terminology in the context in which it is now claimed, the claims are vague and indefinite.

43. Claims 8 and 9 depend from claim 3 and recite that "for all said assays", "one of the antibodies" is obtained by immunization with a specific peptide and "the other" antibody is obtained by immunization with another specific peptide. Claim 3 recites that the immunoassay may either use a solid phase-bound competitor or alternatively may be a sandwich assay that uses at least two antibodies. Although the references to "one of the antibodies" and "the other" antibody are understandable in the context of the aforementioned sandwich assay, there is insufficient antecedent basis for the recitation of two antibodies in the context of the assay involving a solid phase-bound competitor. It is not clear what is meant by "one of the antibodies"

and "the other antibody" for this type of assay, as the claims do not previously recite that two antibodies are used (and typical competitive assay formats do not make use of two antigen-specific antibodies).

44. Claim 9 recites that the other antibody "can be" bound selectively to a solid phase, which renders the claim indefinite because it is not a positive recitation. It is unclear whether the antibody is actually bound to the solid phase or not.

45. Claim 10 recites the limitations "the first antibody", "the second antibody", and "the resulting sandwich complexes". There is insufficient antecedent basis for these limitations in the claim. As discussed with respect to claims 8-9 above, the reference "both the first and the second antibodies" in the context of "all said assays" is unclear since only one of the assays recited in claim 3 is specified to involve more than one antibody.

46. Claim 23 recites the limitation "the order of magnitude of 2X times said level in a healthy person". There is insufficient antecedent basis for this limitation in the claims. In addition, it is unclear what is meant by "an order of magnitude which is greater than the order of magnitude of 2X times said level in a healthy person". Because of the repetition of the terminology "order of magntitude", it is not clear what two parameters are being compared.

47. Claim 26 recites the limitation "said biological fluid" in line 7. There is insufficient antecedent basis for this limitation in the claims.

48. Claims 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which a disease is diagnosed.

Claim 27 recites a method "for the diagnosis of a disease other than sepsis" and concludes with the step of "correlating said level of said mind-regional [sic] partial peptide with the presence of said disease". However, the claim lacks an active method step in which the subject is actually diagnosed with disease.

Claim Rejections - 35 USC § 102

49. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

50. Claims 1-4, 6-10, 15-16, 19-23, 25-29, and 31-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Bougueleret et al. (US 2007/0082363 A1, of record).

Bougueleret et al. teach diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19") and other so-called "cardiovascular disorder plasma polypeptides" or CPPs) (see especially claims 1-5 and paragraphs 12-14, 28, 35, 63-68, 140-161, 168-212). SEQ ID NO:3 as taught by Bougueleret et al. is identical to instant SEQ ID NO:3 (see Figure 1 of the reference and the Examiner's sequence search results via SCORE). Quantification may be via sandwich or "double determinant" ELISA assays that use two antibodies, one of which is labeled directly or indirectly (paragraph 177 on page 27).

With respect to the limitation in claim 1 that the antibodies are specific "only" to the partial peptide, Bougueleret et al. discuss how the antibodies are preferably "specific" for the CPPs of the invention and do not bind other peptides with high affinity [0168]. As the antibodies disclosed in the instant specification are also taught as being "specific", and because there is no apparent difference in the manner in which the antibodies are produced (see discussion in regards to claim 8 below), it is presumed that the prior art antibodies would also possess the same properties as Applicants'. Similarly, it is presumed that the prior art antibodies would not bind to any other epitope of pro-adrenomedullin (as recited in claim 19).

With respect to claim 4, the reference teaches assaying SEQ ID NO:3 in plasma (see, e.g., paragraphs 35, 207, and claim 5).

With respect to claims 6-7, the reference teaches both polyclonal and monoclonal antibodies [0154], [0157]; the former may be purified by immunoaffinity chromatography [0155].

With respect to claim 8, Bougueleret et al. teach that anti-CPP antibodies may be made by immunizing mammals with the CPP or a fusion protein thereof [0154], [0157], i.e., in this case CPP 19 or SEQ ID NO:3. Since the claim employs open transitional language to indicate that the eliciting antigen "comprises" amino acids 68-86 or 83-94 of pre-proAM, this would encompass antibodies raised against an antigen that is SEQ ID NO:3 *per se* as in Bougueleret et al.

Although Bougueleret et al. do not specifically mention that the CPP protein used to raise antibodies is "synthetic", it is noted that the claim does not require that the indicated steps actually be performed in the method. Rather, the limitations as to specific synthetic peptide

sequences convey product-by-process limitations relating to the process by which the antibodies used in the detection method are made. Applicant is reminded that the patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Considering the structure implied by the process steps recited, no structural differences are disclosed or apparent in the resulting antibodies through the use of a synthetic SEQ ID NO:3 vs. that obtained by other means.

Therefore, although the reference is silent as to the specific synthetic sequences recited in instant claim 8, since the recited process reads on producing antibodies against SEQ ID NO:3 *per se*, and because no structural differences are apparent through the use of "synthetic" eliciting antigens, the teachings of Bougueleret et al. read on the claim since the prior art process for producing antibodies is indistinguishable from that recited.

With respect to claim 9, the double determinant ELISA discussed above involves coating the non-labeled antibody on a solid support (paragraph 177 on page 27).

With respect to claim 10, the double determinant ELISA involves a solid support bound to the first antibody (i.e., first labeling component) and a label such as peroxidase (i.e., second labeling component) bound to the second antibody.

With respect to claim 15, which recites that the adrenomedullin determination is "used for diagnosis of a cardiac disease", it is noted that the claim does not clearly call for any additional active method steps to be performed. As such, the claim can be interpreted as simply

referring to a possible intended downstream use of the claimed method and does not impart additional patentable weight.

With respect to claim 16, the reference teaches determining SEQ ID NO:3 in combination with other cardiovascular disorder plasma polypeptides or CPPs [0213].

With respect to claim 23, it is noted that the claim does not clearly require an active method step in which levels are measured from a sample taken from a patient suffering from sepsis. As such, the claim may be interpreted as a statement regarding inherent properties of the assay; i.e., that when the assay is used for this intended purpose, it would produce a measured value as claimed. Since the assay of Bougueleret et al. is indistinguishable from the claimed assay as detailed above, it is presumed that the prior art assay would also be capable of performing as claimed even though the reference is silent with respect to sepsis.

Claim Rejections - 35 USC § 103

51. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

52. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bougueleret et al. in view of Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 53, 60-61, 72-76, and 578-579).

Bougueleret et al. is as discussed above, which teaches sandwich or "double determinant" ELISA methods to detect SEQ ID NO:3, but fails to specifically teach that the two antibodies used in the assay bind to a region of the peptide that extends from amino acid 60 to amino acid 90 of pre-proAM. However, as discussed above, this region corresponds to the C-terminal region of SEQ ID NO:3.

Harlow & Lane teach laboratory procedures involving antibodies, including immunoassays. For example, the reference teaches that one of the most useful immunoassays is the two-antibody sandwich technique, which can be used to determine antigen concentration in a quick and accurate manner (pages 578-579). Such sandwich immunoassays require two antibodies that bind to non-overlapping epitopes on the antigen; either two monoclonal antibodies or one batch of affinity-purified polyclonal antibodies can be used (ibid). The first antibody is bound to a solid phase, while the second antibody is labeled (see diagram on the bottom of page 578, and page 579).

Therefore, in light of the teachings of Harlow & Lane that is routine in the art to use synthetic peptides as immunogens in order to raise antibodies, and that carboxy-terminal sequences are suggested for designing such peptides since they are likely to be immunogenic, it would have been obvious to arrive at the claimed invention by designing peptides corresponding to carboxy-terminal sequences of SEQ ID NO:3 and raising antibodies against such peptides. One would have had a reasonable expectation of success because Harlow & Lane teach that a surprisingly high percentage of antibodies raised using carboxy-terminal sequences will recognize the native protein.

53. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bougueleret et al. in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

Bougueleret et al. is as discussed above, which teaches diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19"). Bougueleret et al. teach detection via sandwich or "double determinant" ELISA assays that use two antigen-specific antibodies, one of which is labeled directly or indirectly (paragraph 177 on page 27).

The teachings of Bougueleret et al. differ from the instantly claimed invention in that the reference fails to specifically teach that the labeling system comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the double determinant ELISA assay of Bougueleret et al. so as to use the rare earth cryptate labeling system of Mathis et al. (which produce fluorescence emission) In particular, it would have been

obvious to label one of the antibodies in the sandwich assay of Bougueleret et al. with Eu^{3+} cryptate and the other with allophycocyanin as taught by Mathis et al. in order to detect SEQ ID NO:3 in a homogeneous sandwich assay. Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect SEQ ID NO:3 in the method of diagnosing cardiovascular disease of Bougueleret et al.

One would be motivated to do this in light of the teachings of Mathis et al. that the use of rare earth cryptates as fluorescent labels in immunoassays allows for homogeneous assays (i.e., no separation steps). Therefore, one would be motivated to perform a sandwich immunoassay for SEQ ID NO:3 using the labels of Mathis et al. so as to eliminate the need for separation or wash steps needed for typical ELISA procedures (such as that of Bougueleret et al.). Furthermore, one would have been motivated to detect SEQ ID NO:3 by the homogeneous fluoroassay of Mathis et al. in order to allow for an assay that is free from media interactions.

One would have had a reasonable expectation of success because Mathis et al. also teaches that labeling of different types of molecules was done with ease (page 1395, "Discussion").

54. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bougueleret et al.

Bougueleret et al. is as discussed above, which teaches diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19"). However, the reference does not make explicit that the method is performed on those subjects who are "not suspected of suffering from sepsis".

Nonetheless, because the assay of Bougueleret et al. is taught in the context of *cardiovascular disease,* it would have been obvious to perform the assay on those subjects suspected of suffering from cardiovascular disease rather than those suspected of having other diseases such as sepsis.

Double Patenting

55. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

56. Claims 1, 15-16, 19-29, and 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/997250. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '250 application also claims a method of detecting the concentration of the midregional proadrenomedullin partial peptide having amino

acids 45-92 of preproadrenomedullin in biological fluids (see especially claims 1 and 3). The peptide may be measured by sandwich immunoassay (see claim 4), may be measured in plasma (see claim 11), and other parameters may be measured as part of a multi-parameter determination (see claims 7-10). Although instant claims 15-16 recite that the determination of adrenomedullin is used in the area of cardiac diagnosis, while the copending application relates to neurodegenerative disorders, as discussed above the instant claims do not clearly require that any additional active method steps be performed. Therefore, the claims of the copending application, in which the adrenomedullin partial peptide having amino acids 45-92 of preproadrenomedullin is measured in a biological fluid, read on the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

57. Claims 1, 15-16, 19-29, and 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/937061. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '061 application also claims a method of determining the level of pro-adrenomedullin or partial peptides or fragments thereof for *in vitro* diagnosis of patients post-myocardial infarction (see claim 1). The peptide fragment may be MR-proADM (see claim 2), which is the same peptide as the instantly recited SEQ ID NO:3 (see the specification of the '061 application at [006], which defines "MR-proADM as the peptide comprising amino acids 45-92 of preproADM). The '061 application also claims that additional markers can also be determined (i.e., multi-parameter determination). See claims 4-15.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

58. Claims 1, 15-16, 19-29, and 31-32 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/374,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. 12/374,757 also claims a method in which the concentration of mid-proAM ("MR-proADM") is determined by sandwich immunoassay (see especially claims 1-4).

With respect to claims 27-29, which recite diagnosis of a disease other than sepsis, it is noted that the instant specification defines "diagnosis" so as to encompass monitoring of treatment (see [002] of the published application), which is the same purpose for which the method of the copending application is performed (see preamble of claim 1). In particular, Application No. 12/374,757 teaches a method for assessing changes in concentration due to treatment for *cardiac insufficiency*.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

59. Claims 1, 15-16, 19-29, and 31-32 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/305,088. Although the conflicting claims are not identical, they are not patentably distinct from each other because copending Application No. 12/305,088 also claims a

method of determining the concentration of a midregional proADM fragment (MR-proADM) which comprises the amino acids 45-92 of pre-proadrenomedullin (i.e., mid-proAM). See in particular claims 1, 5, and 8. Biological fluid samples assayed may be blood, serum or plasma (claim 6). The method can be conducted using sandwich-type immunoassays (claim 10).

With respect to claims 27-29, Application No. 12/305,088 claims a method for detection or prognosis of neurodegenerative diseases.

60. Claims 2-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-12 of copending Application No. 11/997250; claims 1-17 of copending Application No. 11/937061; claims 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Harlow & Lane.

The '061 application fails to specifically recite that MR-proADM is detected by sandwich immunoassay. The '250, '088 and '757 applications recite a sandwich immunoassay (claims 4), but does not specifically mention that the assay uses a labeled analyte-specific antibody. The copending applications also fail to specifically recite that the antibodies for the sandwich immunoassay bind to a region on mid-proAM that extends from amino acids 60-94 of pre-proAM, or that the antibodies are obtained by immunization with the synthetic peptides recited in claim 8.

The teachings of Harlow & Lane are discussed in detail above.

Regarding claims 2-3 and 9, it would have been obvious to arrive at the claimed invention by employing the sandwich immunoassay format of Harlow & Lane to detect MR-

proADM in the methods of the copending applications. One would also be motivated to do this in light of the teachings of Harlow & Lane that sandwich immunoassays are one of the most useful immunoassays, being quick and accurate.

It would have been further obvious to select either monoclonal or affinity-purified polyclonal antibodies for such a sandwich immunoassay (as in claims 6-7) since Harlow & Lane teach that both of these produce excellent signal strength and specificity.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 *per se* "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

61. Claims 2-3, 6, and 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-12 of copending Application No. 11/997250; claims 1-17 of copending Application No. 11/937061; 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Mathis et al.

The '061 application fails to specifically recite that MR-proADM is detected by sandwich immunoassay. The '250, '757, and '088, applications recites sandwich immunoassays (claims 4), but does not specifically mention that the assay uses a labeled antibody. The copending applications also fail to recite an immunoassay that involves a labeling system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

In light of the Mathis et al. discussed in detail above, it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 (MR-proADM, SEQ ID NO:3) in the methods of the copending applications by the fluoroimmunoassay of Mathis et al. in the method of Bergmann et al. In particular, it would have been obvious to use two monoclonal antibodies against the antigen (i.e., pro-adrenomedullin 45-92) and to label one of the antibodies with Eu^{3+} cryptate (i.e., rare earth cryptate) and the other with allophycocyanin (i.e., fluorescent cyanine-type dye). Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect MR-proADM in the methods of the '250 or '061 applications. One would be motivated to do this in order to detect pro-adrenomedullin

45-92 in a homogeneous assay, requiring no separation steps. One would also be motivated to use the Mathis et al. fluoroimmunoassay in order to avoid the need to use radioactive labels.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

62. Applicant's arguments filed 9/29/2008 have been fully considered.

63. With respect to the objections to the specification, no arguments traversing the objections could be found as part of Applicant's Reply. No amendments have been made to the specification. The objections are therefore maintained for reasons of record as set forth above.

64. With respect to the rejections under § 112, 2nd paragraph which have been reiterated above, no arguments traversing the rejections could be found as part of Applicant's Reply. Accordingly, the rejections are maintained for reasons of record as set forth above.

65. With respect to the rejections under § 102 and § 103 over Bougueleret et al., Applicant argues that the reference is not prior art in view of the certified English translation of the foreign priority document (Reply, page 18). Although the certified English translation submitted on 9/29/2008 is acknowledged, the claims are not entitled to the earlier filing date. In particular, the claims are considered to present new matter for reasons detailed in the rejections under § 112, 1st paragraph above. Support for the noted limitations could also not be found in the foreign priority document for the same reasons. Therefore, the rejections are maintained for reasons of record because Bougueleret et al. is prior art.

66. With respect to the provisional double patenting rejections over copending Application Nos. 11/997250 and 11/997250, no arguments traversing the rejections could be found as part of Applicant's Reply. Accordingly, the rejections are maintained for reasons of record as set forth above.

Conclusion

67. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

68. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571)

272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641